As a preliminary matter, Applicants would like to thank the Examiner for indicating that the rejection of claims 27-28, 33, 34 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Simon et al., Arnold, Jr. et al. or Agrawal et al. in view of Hanecak et al., Vlassov et al. and Milligan et al. has been withdrawn.

For convenience the Examiner's rejections are addressed in the order in which they were presented in the October 22, 2002 Office Action. Reconsideration is respectfully requested.

Priority claim

The present claim of priority has been denied. All rejections in view of the art cited in previous Office Actions have been withdrawn. As best understood by Applicants, priority as presently claimed is not necessary to overcome the prior art rejections. Applicants request clarification if this is not the case.

Provisional Double Patenting

Claims 27-29 and 34 stand provisionally rejected under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over claim 34 of copending Application no. 08/847,151 (Prior Application) Additionally, claim 29 stands provisionally rejected under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over claim 34 of copending Application no. 08/847,151 in view of Milligan, (*Journal of Medicinal Chemistry*, July 1993, Vol. 36, No. 14, pp. 1923-37) ("the Milligan reference"). Applicants submit that this rejection is moot, as the Prior Application became abandoned on December 17, 2002. Accordingly, Applicants request withdrawal of this rejection.

Rejection under 35 U.S.C. § 112, enablement

Claims 27-29 and 34 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly not enabled for a "method of modulating the expression of any and/or all target genes comprising the alimentary administration of antisense oligonucleotides comprising 2' MOE modifications." The Office Action, however, specifically acknowledges that the specification is enabling for "enhanced bioavailability of antisense oligonucleotides comprising 2'-O-(2-methoxyethoxy) modifications (2'MOE)." (Office Action at p.3-4). In view of the Examiner's indication that 2'-MOE modifications are enabled by the present specification, Applicants have amended the claims to recite such a 2' modification. Applicants submit the following discussion of state of the art, which exemplifies the predictability of art of antisense treatment, and bolsters the Examiner's statements with respect to the enablement of the claims as presently amended.

The Office Action cites Crooke *et al.*, *Antisense Res. and Application*, 1, pp.1-50 (1998), Pihl-Carey, *BioWorld Today*, 10, pp.1-2 (Dec. 16, 1999), Branch, *Trends in Biochem. Sci.*, 23, pp. 45-50 (1998), and Palu *et al.*, *J. of Biotechnology*, 68, pp. 1-13 (1999) for the proposition that there are many obstacles to successful antisense treatment, thereby making the art highly unpredictable. In response, Applicants respectfully traverse.

The enablement requirement of 35 U.S.C. § 112 mandates that the specification teach those skilled in the art how to make and use the claimed invention without undue experimentation. *See In re Wands*, 8 U.S.P.Q.2d 1400 (Fed. Cir. 1988). The test of enablement is **not** simply whether experimentation would have been necessary, but whether such experimentation would have been **undue**. *See In re Angstadt*, 190 U.S.P.Q. 214, 219 (C.C.P.A. 1976). The fact that experimentation may be complex does not necessarily make it

undue, if the art typically engages in such experimentation. *See Wands*, 8 U.S.P.Q.2d at 1404. The factors to be considered in determining whether any necessary experimentation is undue include:

i. the breadth of the claims;
ii. the nature of the invention;
iii. the state of the prior art;
iv. the level of one of ordinary skill;
v. the level of predictability in the art;
vi. the amount of direction provided by the inventor;
vii. the existence of working examples; and
viii. the quantity of experimentation needed to make or use the invention based on the content of the disclosure.

Id. (citing *Ex parte Forman*, 230 U.S.P.Q. 546, 547 (Bd. Pat. App. & Int. 1986)). Any conclusion of non-enablement must be based on the evidence as a whole. *Id.*

Applicants respectfully note that the Examiner bears the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention. *In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993) (examiner must provide reasonable expectation as to why scope of protection provided by claim is not adequately enabled by disclosure); MPEP §2164.04. The MPEP further states that a specification **must** be taken as being in compliance with the enablement requirement of 35 U.S.C. § 112, first paragraph, unless there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support. *Id.* at 224. The MPEP also quotes *In re Marzocchi*, which states in relevant part:

> [I]t is incumbent on the Patent Office, whenever a rejection on this basis is made, to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement. Otherwise, there would be no need for the applicant to go to the trouble and expense of supporting his presumptively accurate disclosure.

439 F.2d at 224, 169 USPQ at 370. Applicants believe that the present rejection does not meet the *Marzocchi* standard, as articulated in the MPEP, for at least two reasons. First, the Office Action has inaccurately characterized the state of the art of antisense oligonucleotide chemistry. Second, the Office Action takes the strained position that Applicants must do more than enable practice of the claimed methods in order to comply with the first paragraph of 35 U.S.C. § 112.

I. The Office Action Has Inaccurately Characterized the State of the Art of Antisense Oligonucleotide Chemistry

The present invention is, in part, the discovery that certain chemical modifications, when made to an antisense oligonucleotide, improve the bioavailability of that oligonucleotide. An antisense oligonucleotide is a short oligonucleotide that is synthesized to bind to a target RNA or DNA sequence in order to modulate its expression. Several factors influence the ability of an antisense oligonucleotide to bind to its target nucleic acid and thereby modulate its expression. One such factor is the ability of the antisense oligonucleotide to reach its target site. An antisense oligonucleotide that is present in increased amounts, *e.g.*, has greater bioavailability, will necessarily have a greater ability to reach its target site, bind to its target nucleic acid, and subsequently modulate expression of the target nucleic acid. Accordingly, the present claims are directed to methods of modulating the expression of a target nucleic acid by administering an improved oligonucleotide, *e.g.*, an oligonucleotide comprising a 2' modification.

The Office Action takes the position that the state of the art of antisense technology is unpredictable and for that reason concludes that the specification does not provide enablement to modulate expression of any and/or all target genes in an organism. The claims

as amended, are directed to oligonucleotides with a 2'-MOE modification, which the Office Action acknowledged was enabled. The Office Action relies on four references to suggest that antisense technology is unreliable. Applicants submit that the Office Action misinterprets these four references. The cited references, at most, express the sentiment that not every antisense molecule will be therapeutically effective. The cited references do not suggest that antisense technology is unpredictable. For example, the Office Action relies on the Pihl-Carey reference, *BioWorld Today, supra*, for the proposition that the state of the art of antisense oligonucleotides is unpredictable. This article, however, implies no such thing. Instead, it demonstrates that not all antisense oligonucleotides will successfully complete Phase III clinical trials. The ability of a putative drug to successfully complete Phase III clinical trials, however, is in no way required for enablement commensurate with the requirements of 35 U.S.C. § 112, first paragraph. According to MPEP § 2107.03, "Office personnel should not impose on applicants the unnecessary burden of providing evidence from human clinical trials .... [I]t is improper for office personnel to request evidence...regarding the degree of effectiveness [in humans] (emphasis in the original)." Enablement requires only that the application teach how to make and use the invention without undue experimentation.

As evidence of the ***predictable*** state of the art of antisense technology, Applicants herewith submit selected chapters form a book entitled Antisense Drug Technology (Marcel Dekker, Inc., (2001)). Antisense Drug Technology is replete with routine instructions and guidelines that can be used by a skilled practitioner to synthesize antisense oligonucleotides capable of binding target nucleic acids. For example, Chapter 5, entitled "Methods of Selecting Sites in RNA for Antisense Targeting" (Exhibit A), and the supporting references cited therein, illustrate that those skilled in the art do indeed consider antisense

oligonucleotide chemistry to be predictable. For example, page 111, states that "[o]ne attraction of antisense technology is that high specificity can be achieved." The references that are citied in support of this statement, *i.e.*, references 11, 63, and 64, were published from 1994 to 1999. Accordingly, Chapter 5 of Antisense Drug Technology, along with the supporting references cited therein, teach that the state of the art of antisense oligonucleotide chemistry is indeed predictable and that those skilled in the art would not have had to partake in undue experimentation to achieve binding specificity.

Likewise, Chapter 7 of Antisense Drug Technology entitled "Suborgan Pharmacokinetics" and the references listed therein (Exhibit B) teach that the efficacy and safety of certain oligonucleotides in various animal models and in the clinical setting have been well documented (p.155). Chapter 7 further teaches that, in various animal models, not only can oligonucleotides be given directly without a carrier, but that such oligonucleotides are consistently (*i.e.*, ***predictably***) and unequivocally localized within the cells of various organs. Chapter 8 summarizes the art with respect to modulating the activity or production of proteins with respect to human subjects (Exhibit C). Accordingly, Chapters 6 and 8 of Antisense Drug Technology, along with the supporting references cited therein, teach that the state of the art of antisense oligonucleotide chemistry is indeed predictable and that those skilled in the art do not have to partake in undue experimentation to modulate the production or activity of a protein in an organism, thus directly contradicting the allegations of non-enablement in the Office Action.

Another reference demonstrating the predictability of antisense technology is Whitesell *et al., Antisense Res. Dev.* (1991) 1:343-50 (hereinafter referred to as "Whitesell") (Exhibit D). Whitesell teaches that those skilled in the art as far back as 1991 successfully performed *in vivo* modulation of N-myc expression in mice. Similarly, Mirabelli *et al., Anti-*

Cancer Drug Des. (1991), 6, 647-661 ((hereinafter referred to as "Mirabelli") (Exhibit E) evidences the state of the art as far back as 1991. At page 651, fourth full paragraph, Mirabelli notes that "the therapeutic indexes of phosphorothioate oligonucleotides appear to be quite high" and that "certain phosphorothioates . . . are extremely well tolerated in animals." Accordingly, Whitesell and Mirabelli provide evidence that the state of the art of antisense oligonucleotide chemistry was not as embryonic at the time of filing the present application as the Office Action would lead one to believe. Moreover, Whitesell and Mirabelli provide evidence that as far back as 1991, one skilled in the art would not have to conduct undue experimentation to modulate the production or activity of a protein in an organism.

Yet another reference demonstrating the state of the art is *Ann. Rev. Pharmacol. Toxicol.* 1992, 32:329-76 ((hereinafter referred to as "Crooke") (Exhibit F). Crooke is a 1992 review of the art and, at page 342, provides evidence that those skilled in the art were conducting *in vivo* pharmacokinetic data in mice and rats.

Still another reference is Cossum *et al.*, *The Journal of Pharmacology and Experimental Therapeutics* (1993) 267:1181-1190 ((hereinafter referred to as "Cossum") (Exhibit G). Cossum discusses non-antisense effects and ways to avoid them *in vivo* by not using doses that are significantly greater than the antisense effective dose. Thus, by 1993, the skilled artisan knew how to avoid non-specific effects. Moreover, Cossum evidences that, by 1993, those skilled in the art were delivering antisense oligonucleotides *in vivo* where the only carrier was a phosphate buffer.

Moreover, a handful of oligonucleotide antisense molecules have, in fact, successfully completed phase III trials and been FDA approved. For example, the oligonucleotide antisense drug Fomivirsen (ISIS Pharmaceuticals, Inc. ("ISIS"), the assignee of the instant

application) was approved for treatment of cytomegaloviral-induced retinitis by the FDA in 1998. The Investigational New Drug Application ("IND") for Fomivirsen was filed with the FDA back in 1993. Many other oligonucleotide antisense drugs are currently involved in clinical trials (*see, e.g.*, Tamm *et al.* (the Lancet (2001) 358:489-497 at 490))(Exhibit H).

Significantly, a search of the art of antisense oligonucleotides reveals approximately 16,986 references that comprise the "state of the art" of antisense oligonucleotide chemistry (*see* Exhibit I). Given the wealth of information pertaining to antisense technology, the Office Action has clearly ignored the state of the art ***as a whole*** and has mischaracterized it as unpredictable. Whether or not every antisense oligonucleotide will make a good drug is not relevant to a determination of unpredictability. Accordingly, Applicants respectfully request that the rejection of the claims for alleged lack of enablement be withdrawn.

II. The specification provides sufficient guidance to practice the claimed invention.

After reviewing the pending claims, the Examiner should find this invention does not require undue experimentation. As stated in the MPEP, "the presence of inoperative embodiments within the scope of a claim does not necessarily render a claim nonenabled. The standard is whether a skilled person could determine which embodiments that were conceived, but not yet made, would be inoperative or operative with expenditure of no more effort that is normally required in the art." MPEP 2164.08(b).

As evidenced by the drug Fomivirsen and other antisense oligonucleotides that are in clinical trials, those skilled in the art have proven that antisense oligonucleotides do routinely bind to their target molecules and modulate expression. As demonstrated by the provided references, methods of determining whether a putative oligonucleotide will bind to a target nucleic acid are well known. Accordingly, it would be routine for a skilled practitioner to

choose an oligonucleotide of interest, modify the oligonucleotide using the methods described in the present specification, and determine whether the oligonucleotide as modified binds to a target nucleic acid and modulates its expression. Whether the modulation will rise to the level of therapeutic efficacy is not the standard by which to measure whether one skilled in the art could practice the present invention.

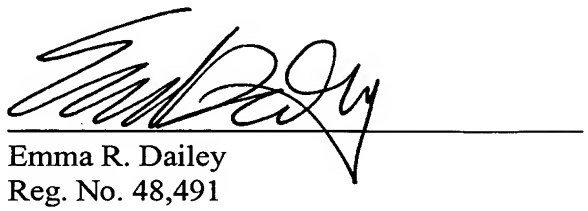
The specification is replete with examples of how to modulate the expression of genes using the methods of the present invention. The Office Action acknowledges that the "specification teaches the enhanced bioavailability following alimentary administration of 2'-MOE gapped oligonucleotides compared to phosphorothioate containing, but non-2'-MOE containing oligonucleotides" (Office Action, p.5). Example 1 of the specification, for example, teaches that one method of modulating the expression of protein kinase C-α includes choosing an oligonucleotide known to inhibit protein kinase C-α expression, synthesizing the oligonucleotide with a 2' modification of the present invention, and administering the oligonucleotide to a mammal. In figure 2, the Applicants demonstrate that the 2' modified oligonucleotide has increased bioavailability in the mammal as compared to the unmodified oligonucleotide. In Example 4 of the specification, Applicants choose an oligonucleotide targeted to human C-raf that has been shown to be extremely effective in inhibiting raf expression in *vitro* and in *vivo*. After synthesizing the oligonucleotide with a 2' MOE modification, Applicants demonstrate that the modified oligonucleotide has greater rates of absorption in rat intestine as compared to the unmodified oligonucleotide.

Accordingly, after reading the specification, a skilled practitioner would understand that one method of modulating expression of a target nucleic acid includes choosing an oligonucleotide of interest known to have activity, modifying it according to the methods of the present invention, and administering it to a mammal. Once introduced into the mammal,

the oligonucleotide will have its intended effect as demonstrated by the bioavailability studies. Accordingly, Applicants submit that the practice of the present invention does not require undue experimentation and respectfully request that the rejection under 35 U.S.C. § 112, first paragraph, be withdrawn.

The foregoing represents a *bona fide* attempt to advance the present case to allowance. Applicants submit that this application is now in condition for allowance. Accordingly, an indication of allowability and an early Notice of Allowance are respectfully requested. If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 215-568-3100.

Date: **February 21, 2003**



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APPENDIX A

VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Claims

Please cancel claims 27 and 34, without prejudice, and add claims 35 and 36 presented in the body of the amendment. Please amend claims 28 and 29 as presented below:

28 (Amended). The method of claim 35 [27] wherein said administration into the alimentary canal is oral, rectal, endoscopic, sublingual or buccal administration.

29 (Amended). The method of claim 36 [34] wherein said heteroatomic backbone modification is a methylene(methylimino) modification.

APPENDIX B

CLAIMS SUBJECT TO EXAMINATION PRIOR TO ENTRY OF THE AMENDMENT SUBMITTED HEREWITH

27. A method of modulating expression of a target nucleic acid comprising administering into the alimentary canal an effective amount of an oligonucleotide comprising a 2'-modification, wherein said 2'-modification comprises the formula $(O\text{-}CH_2\text{-}CH_2)_n\text{-}O\text{-}$alkyl, and wherein said oligonucleotide hybridizes to said target nucleic acid, and modulates the expression thereof.

28. The method of claim 27 wherein said administration into the alimentary canal is oral, rectal, endoscopic, sublingual or buccal administration.

29. The method of claim 34 wherein said heteroatomic backbone modification is a methylene(methylimino) modification.

34. A method of modulating expression of a target nucleic acid comprising administering into the alimentary canal an effective amount of an oligonucleotide comprising a 2' modification, wherein said 2' modification comprises the formula $(O\text{-}CH_2\text{-}CH_2)_n\text{-}O\text{-}$alkyl, and a heteroatomic backbone modification, wherein said oligonucleotide hybridizes to said target nucleic acid, and modulates the expression thereof.